# Cancer Modes of Action and Dose-Response for Inorganic Arsenic

**Presented by**

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# Purpose

❑ IRIS contains an inorganic arsenic cancer slope factor for skin cancer based on studies published in the 1960s.

❑ For a drinking water arsenic regulation EPA derived a cancer risk assessment in January 2001 based on the 1999 NRC recommendations.

❑ In 2001 the Agency asked NRC to consider new studies and their impact on EPA's arsenic risk assessment.

❑ In September 2001, NRC issued its 2001 update.

# Arsenic Cancer Slope Factor Workgroup

❑ An intra-Agency workgroup examined the NRC (2001) recommendations and their potential influence on regulation of inorganic arsenic by the various program offices.

- Office of Water
- Office of Research and Development
- Office of Pesticide Programs
- Office of Children's Health Protection
- Office of Solid Waste
- Office of Emergency Response and Remediation.

# Issues To be Discussed in This Presentation

❑ **Metabolism of inorganic Arsenic**

❑ **Mode of Action:  Impact of Low-Dose Extrapolation**

❑ **Data Set Selection for Assessing Cancer Potency**

❑ **Data Interpretations for Data Set Selected**

- **Estimate dietary intake of arsenic**

- **Estimate drinking water rate**

❑ **Model Implementation for Estimating Cancer Potency**
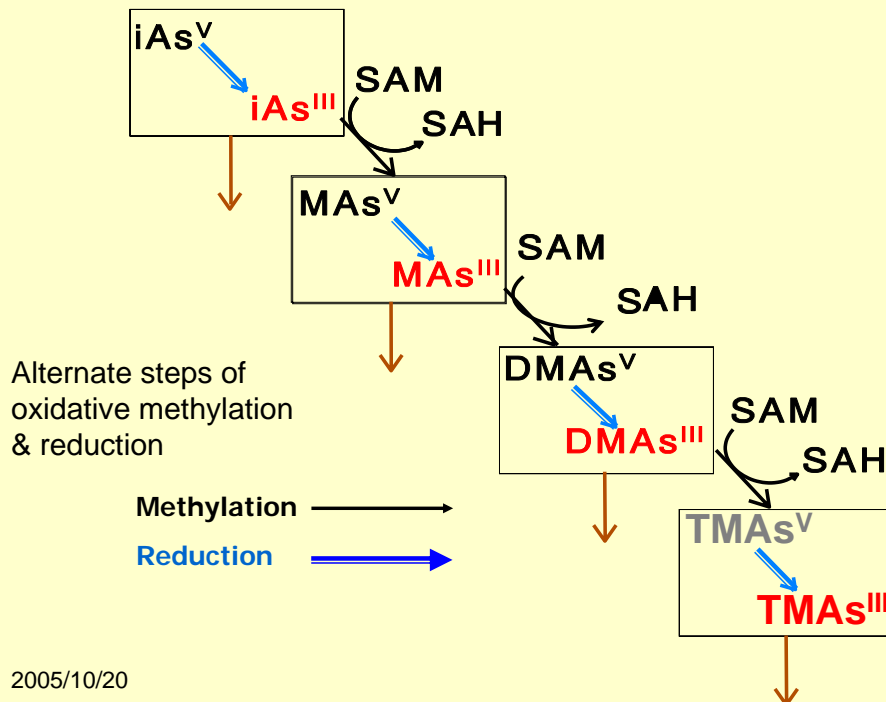
# Metabolism of Inorganic Arsenic

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## Inorganic Arsenic – Carcinogenic Effects

❑ Human:
- Skin, Bladder, Lung, Liver, Kidney, Prostate

❑ Animal:
- Very high doses (no good animal model for inorganic arsenic-related human cancer)

# Metabolism of Arsenic

$iAs^V$

$iAs^{III}$

SAM

SAH

$MAs^V$

$MAs^{III}$

SAM

SAH

$DMAs^V$

$DMAs^{III}$

SAM

SAH

$TMAs^V$

$TMAs^{III}$

Alternate steps of oxidative methylation & reduction

Methylation ⟶

Reduction ⟶

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# Arsenic – Metabolism (*Continued*)

❑ Urinary metabolites (human): 10-30% inorganic arsenic, 10-20% MMA, 60-80% DMA

❑ Urine- North east Argentina (Concha et al. 1998):

  Women    2% MMA,  58-74% DMA
  Children    3.6% MMA, 47-54% DMA

❑ North east Taiwan – 27% MMA  (Chiou et al. 1997)

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# Arsenic – Metabolism

❑ Variation between species and among human populations in the rate and extent of methylation of inorganic arsenic:

- Nutrition
- Sex
- Age
- Life Style (smoking)
- Disease Status
- Genetic Status (Polymorphism)

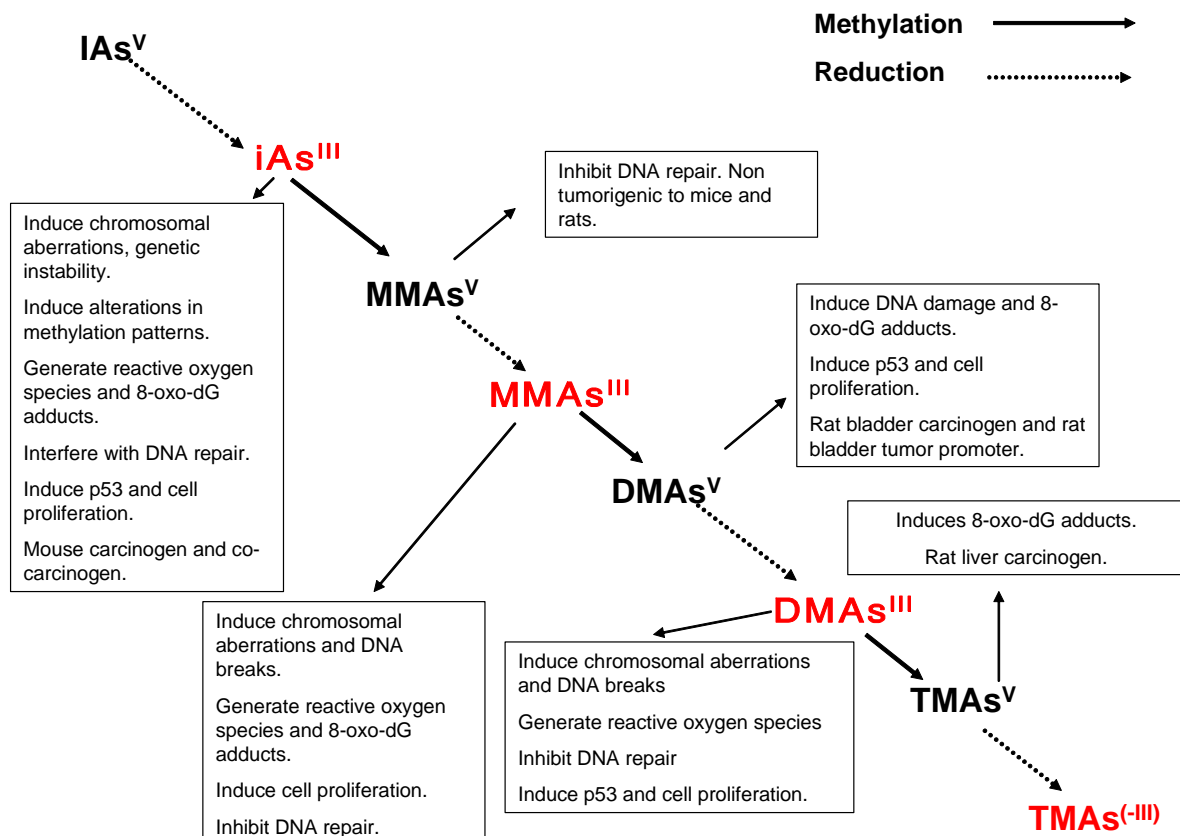# Mode of Action:
# Potential Impact On Low Dose Extrapolation

# Status of Mode of Action

❑ NRC 1999 and NRC 2001 indicated that a single mode of action could not be identified for inorganic arsenic.

❑ EPA believes that this is still true.

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Methylation ⟶
Reduction ·····▸

IAs$^V$

iAs$^{III}$

**Induce chromosomal aberrations, genetic instability.**

Induce alterations in methylation patterns.

Generate reactive oxygen species and 8-oxo-dG adducts.

Interfere with DNA repair.

Induce p53 and cell proliferation.

Mouse carcinogen and co-carcinogen.

MMAs$^V$

Inhibit DNA repair. Non tumorigenic to mice and rats.

MMAs$^{III}$

Induce DNA damage and 8-oxo-dG adducts.

Induce p53 and cell proliferation.

Rat bladder carcinogen and rat bladder tumor promoter.

DMAs$^V$

Induce chromosomal aberrations and DNA breaks.

Generate reactive oxygen species and 8-oxo-dG adducts.

Induce cell proliferation.

Inhibit DNA repair.

DMAs$^{III}$

Induce chromosomal aberrations and DNA breaks

Generate reactive oxygen species

Inhibit DNA repair

Induce p53 and cell proliferation.

Induces 8-oxo-dG adducts.

Rat liver carcinogen.

TMAs$^V$

TMAs$^{(-III)}$

# EPA Retains Linear Extrapolation

❑ Multiple potential modes of action being hypothesized.

❑ Metabolites have distinct toxicities.

❑ Metabolites may vary in modes of action.

❑ Different factors (e.g., polymorphism) affect metabolite production.

❑ Simultaneously exposed to mixtures of multiple metabolites (mixtures assessment).

# Charge Question

Please comment on the conclusion that the available data support the hypothesis that multiple modes of action may be operational following exposure to inorganic arsenic.

# Data Set Selection for Assessing Cancer Potency

# Studies Evaluated by EPA

❑ Northeast Taiwan – Chiou et al. 2001;

❑ Chilean – Ferreccio et al. (2000);

❑ Southwestern Taiwan – Lamm et al 2003

❑ U.S. – Lamm et al. 2004

❑ Western U.S. – Steinmaus et al. 2003

❑ U.S. smelter – Tollestrup et al. 2003

❑ Taiwan – Chen et al., 2004

❑ SW Taiwan –  Chen et al. 1985, Wu et al. 1989

# Data Set Selection

Southwestern Taiwan study (Chen et al. 1985, Wu et al. 1989) used as the primary data source.

❑ Duration of exposure and follow-up.

❑ Size of the population.

❑ Extensive pathology data.

❑ Similar socio-economic lifestyles in the study population.

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# Southwestern Taiwan Study

❑ Exposure: ~1900 – 1966

❑ 42 villages (over 40,000 individuals examined)

❑ Village wells 10-934 ppb.

❑ Mortality for bladder, lung and kidney cancers from 1973- 1986 death certificates.

❑ Known lifestyles (farming, fishing, and salt production).

# NRC (1999, 2001 Update) Conclusions

❑ The southwestern Taiwanese ecological studies are the strongest sources of dose-response information for cancer endpoints.

❑ Focus cancer assessment on arsenic-induced bladder and lung cancers.

❑ Analyze risks of internal cancers both separately and combined.

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# Charge Question

Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans? Please discuss the rationale for your response.

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# Data Interpretations for
# Data Set Selected

# Dietary Intake of Inorganic Arsenic

❏ Arsenic in food (e.g., dry rice, sweet potatoes);

❏ Arsenic from drinking water; and

❏ Arsenic from water used in cooking (e.g., boiling rice and potatoes).

**Translation of Taiwanese Exposure to U.S. Population**

❏ Taiwanese dose from food determined from:
  ■ Types and amounts of food consumed.
  ■ Inorganic arsenic concentration in food.

❏ Taiwanese dose from drinking water from:
  ■ Water consumption rates.
  ■ Inorganic arsenic concentration.

❏ Use dose (from food and water) and body weight to calculate Taiwanese dose (in mg/kg/day).

❏ Equate relative risks per unit dose (in mg/kg/d) in Taiwan and U.S.

# Arsenic in Asian Food

**Food Consumption Studies**
  ❏ Yang and Blackwell 1961 SW Taiwan rice and yams.
  ❏ Watanabe et al. 2004 Bangladesh rice, bread, potatoes, fish.

**Concentration of Arsenic in Food**
  ❏ Li et al. 1979 Taiwan 0.3-0.53 mg/kg rice.
  ❏ Schoof et al. 1998 SW Taiwan 0.15 mg/kg rice, 0.11 mg/kg yams.
  ❏ Duxbury et al. 2003 Bangladesh 0.1-0.42 mg/kg rice.
  ❏ Bae et al. 2002 Bangladesh 0.17 mg/kg rice.

**Dietary Arsenic from Food Intake**
  ❏ Schoof et al. 1998 50 µg/day.
  ❏ Watanabe et al. 2004. 120 µg/day females, 214 µg/day males.

# Arsenic from Food

❑ EPA ran the model over a range of arsenic consumption rates (0 - 50 µg/day). NRC considered 30 –50 µg/day.

❑ Variation due to food was 2-9 % of arsenic risk (insensitive).

# Charge Question

What background dietary intake of arsenic value does the panel recommend for both the control population and study population of Southwestern Taiwan used in deriving the cancer slope factor for inorganic arsenic?

# Drinking Water Intake

❑ Taiwanese dose from water cannot be directly applied to U.S. population

❑ Consumption differences

  ▪ Climate

  ▪ Activity level

  ▪ Body Weight

❑ Arsenic concentrations in Taiwan are higher than in the U.S.

# Drinking Water Studies

❑ Asia

  ▪ 1961 SW Taiwan 1-3 L/d

  ▪ 1989 SW Taiwan up to 3.75 L/d

  ▪ 2004 Bangladesh 3.1 L/d, max 6 L/d working up to 6 hr/d.

  ▪ 2001 India 3.5 L/d (4.2 L/d ♂; 3.2L/d ♀).

❑ U.S.

  ▪ 1981 0.4-2.4 L/d normal, 2.8-3.4 L/d up to 90°F, 3.7 L/d moderately active.

  ▪ 2004 1 L/day lifetime tap water, 2.8 L/day adults all beverages; 3.2 L/day adult food & beverages

  ▪ 1989 1.4 L/day tap water and 2.1 L/day including food and beverages.

## SW Taiwanese Drinking Water Rate
## (L/day)

| | NRC (2001) | | Draft EPA IRIS | |
|---|---|---|---|---|
| | Taiwan | U.S. | Taiwan | U.S. |
| Male | 2.2 | 1.0 | 3.5 | 2.0 |
| Female | 2.2 | 1.0 | 2.0 | 2.0 |

# Charge Question

What drinking water value does the panel recommend for use in deriving the cancer slope factor for inorganic arsenic?

# Model Implementation for Estimating Cancer Potency

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# NRC 2001 Model Recommendations

❑ **Poisson model with linear dose effect**

❑ **Quadratic age adjustment for Taiwanese**

❑ **Southwest Taiwanese background population**

❑ **BIER-IV formula for US age/mortality adjustment**

# Unit Risks from Model x $10^{-4}$ (ppb)$^{-1}$

| Endpoint | Sex | NRC 2001 Tables 5-7, 5-8 | Draft IRIS Tables 5-4 – 5-7 |
|----------|-----|--------------------------|------------------------------|
| Lung | M | 1.4 | 1.4 |
| Lung | F | 1.8 | 1.2 |
| Bladder | M | 2.3 | 0.4 |
| Bladder | F | 1.2 | 0.3 |

# Charge Questions

❑ Does the panel concur with the selection of a linear model following the recommendations of the NRC (2001) to estimate cancer risk at this time? Please discuss your response in light of the highly complex mode of action for iAs with its metabolites.

❑ Please comment upon precision and accuracy of the re-implementation of the model.

# Summary

❑ For arsenic carcinogenicity, several plausible modes of action have been established, different factors affect metabolite production, metabolites vary in modes of action, and each metabolite has distinct toxicity. Therefore, EPA retained linear extrapolation at low doses.

❑ The Southwestern Taiwan studies are the strongest sources of dose-response information for cancer endpoints. EPA has focused its cancer assessment on arsenic-induced bladder and lung cancers.

# Summary (*Continued*)

❑ Because the Southwestern Taiwan studies were selected for the risk assessment, with new available information, EPA used a range of dietary and water intake for the Southwestern Taiwanese population.

❑ EPA decided to use a Poisson model with linear dose effect, age adjustment, mortality adjustment, and background population to estimate the potency of inorganic arsenic.